Addiction Medicine
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Pulmonary Complications of Smoked Substance Abuse

DONALD P. TASHKIN, MD, *Los Angeles*

After tobacco, marijuana is the most widely smoked substance in our society. Studies conducted within the past 15 years in animals, isolated tissues, and humans indicate that marijuana smoke can injure the lungs. Habitual smoking of marijuana has been shown to be associated with chronic respiratory tract symptoms, an increased frequency of acute bronchitic episodes, extensive tracheobronchial epithelial disease, and abnormalities in the structure and function of alveolar macrophages, key cells in the lungs' immune defense system. In addition, the available evidence strongly suggests that regularly smoking marijuana may predispose to the development of cancer of the respiratory tract. "Crack" smoking has become increasingly prevalent in our society, especially among habitual smokers of marijuana. New evidence is emerging implicating smoked cocaine as a cause of acute respiratory tract symptoms, lung dysfunction, and, in some cases, serious, life-threatening acute lung injury. A strong physician message to users of marijuana, cocaine, or both concerning the harmful effects of these smoked substances on the lungs and other organs may persuade some of them, especially those with drug-related respiratory complications, to quit smoking.

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Humans smoke a variety of substances, including tobacco, cannabis (marijuana and hashish), alkaloidal cocaine (freebase cocaine or "crack"), phencyclidine (PCP), heroin, opium, and, most recently, methamphetamine ("ice"). The popularity of these smoked substances is due, no doubt, to the pleasure derived from the psychoactive components within the smoke, such as nicotine in tobacco and Δ^9-tetrahydrocannabinol (THC) in cannabis, which also serve to reinforce the smoking habit through addiction, psychological dependence, or both.

Because the lungs are the principal organ exposed to the combustion products of smoked substances, pulmonary complications would be expected to be prominent among the health consequences of smoking. Tobacco, the most widely smoked substance in our society, has been studied extensively with regard to its adverse effects on the lungs, particularly its link to chronic obstructive pulmonary disease and lung cancer.[1,2] Much less is known about the effects on the lungs of smoking other substances, although a body of evidence is emerging implicating marijuana and crack cocaine as causes of respiratory tract disease. Because there is as yet little published information regarding the pulmonary effects of smoking other illicit substances, this article will focus mainly on our current state of knowledge concerning the respiratory complications of smoking marijuana and alkaloidal cocaine; the latter are the most widely smoked substances in our society except for tobacco, the pulmonary effects of which are already well known.

Marijuana

Recent nationwide surveys show a continued decline in marijuana use[3,4]; nonetheless, marijuana remains one of the most widely abused substances in our society. According to a recent survey,[3] among high-school seniors about 50% were ever users of marijuana, slightly less than 40% used it within the past year, 23% used it within the past month, and 4% (6% of male students) reported using it daily. Although cannabis products are sometimes taken orally, smoking is the preferred route of administration so that the lungs are exposed first and foremost to its combustion products. These products include a number of known respiratory irritants and carcinogens[5,6] and many other compounds of which the pulmonary effects are unknown. The smoke contents of marijuana are similar in many respects to those of tobacco with the major exceptions that marijuana contains Δ^9-THC and about 60 other cannabinoid compounds[5,6] whereas tobacco contains nicotine. That THC is itself a respiratory irritant is suggested by the harsh respiratory sensations elicited by the smoking of high-potency cannabis preparations and the observation that THC administered in pure form as an aerosol generally provokes cough and can cause bronchospasm in patients with asthma.[7] It is also noteworthy that most tobacco cigarettes currently in use are filter-tipped and have a relatively low tar content, but marijuana cigarettes do not contain filters and generate about twice as much tar as tobacco per unit of weight, assuming a similar smoking profile.[8] Furthermore, the techniques for smoking marijuana and tobacco differ

From the Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of California, Los Angeles, School of Medicine.
Supported by United States Public Health Service grant RO1-DA-03018 from the National Institute of Drug Abuse.
Reprint requests to Donald P. Tashkin, MD, Department of Medicine, UCLA School of Medicine, Los Angeles, CA 90024.

ABBREVIATIONS USED IN TEXT

D_LCO = diffusing capacity for carbon monoxide
THC = Δ^9-tetrahydrocannabinol

substantially: on the average, with marijuana the inhalation, or "puff," volume is about two-thirds larger, the depth of smoke inhalation about 40% greater, and breath holding about four times longer than those characteristic of tobacco smoking.[9] These differences in filtration and smoking technique can result in about a fourfold greater amount of tar delivered to and retained in the lungs from the smoking of marijuana than from a comparable amount of tobacco, thus potentially amplifying the harmful effects of marijuana on the lungs.

A wealth of epidemiologic, pathologic, clinical, and experimental studies have established tobacco smoking as the most important cause of lung cancer and chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.[1,2] Because of the rough similarity in smoke contents between marijuana and tobacco and the differences in filtration and smoking techniques that augment delivery of the volatile and particulate contents of marijuana smoke to the respiratory tract, there is concern that the habitual smoking of marijuana may have adverse effects on the lungs similar to those caused by tobacco smoking. The long-term respiratory consequences of tobacco smoking generally do not become clinically apparent until two or more decades after the smoking habit is initiated.[1] Because the habitual smoking of marijuana by a sizable segment of our society is a relatively recent phenomenon compared with regular tobacco smoking, sufficient time may not have transpired for the potentially harmful long-term effects of marijuana smoking on the lungs to become clinically apparent. Nonetheless, the results of studies in animals, isolated tissues, and humans during the past 15 years show that marijuana smoke has injurious effects on the lungs. I have summarized the results of these studies.

Animal and Tissue Studies

In rats with exposure to marijuana smoke for three months in doses comparable with those used by humans, Fleischman and co-workers noted focal inflammatory changes involving the alveoli that progressed to chronic pneumonia after a year of exposure.[10,11] In tracheotomized dogs with exposure to the smoke of four marijuana cigarettes a day for 30 months, Roy and associates found severe inflammation of the peripheral airways and squamous metaplasia of the tracheal epithelium[12]; these changes were more pronounced than those noted after the same duration of daily exposure to a comparable amount of tobacco smoke. In two of ten monkeys, Heath observed fatal respiratory complications after heavy marijuana smoking for 3½ to 5½ months.[13] Huber and colleagues found that the bactericidal activity of rat alveolar macrophages was depressed by a water-soluble component of the gas phase of fresh marijuana smoke and that inactivation of pathogenic bacteria aerosolized into the lungs of rats with exposure to increasing amounts of marijuana smoke was impaired in a dose-dependent manner.[14,15] These findings suggest that marijuana smoking can impair the lungs' host defenses against infection and other noxious insults.

Several lines of experimental evidence suggest that marijuana has the potential for causing cancer of the respiratory tract. First, the smoke of marijuana contains known carcinogens, including a higher concentration of polyaromatic hydrocarbons, such as benzpyrene and benzanthracene, and a comparable amount of the volatile *N*-nitrosamines.[5] Second, in studies involving the Ames *Salmonella* microsome assay, marijuana produced mutations comparable in number with those produced by an equivalent amount of tobacco smoke condensate.[16,17] Third, marijuana smoke condensate (tar) painted on the skin of mice has shown tumorigenicity and tumor-promoting activity.[5,18] Fourth, long-term exposure of hamster lung cell cultures to marijuana smoke induced changes in the genetic material of the cell followed by irregularities in cell division that progressed to malignant transformation within three to six months of exposure; similar but less prominent abnormalities were noted during comparable exposures to tobacco.[19] Because malignant transformation also occurred in the control cultures at 12 to 24 months, the smoke of marijuana (and tobacco) appears to have accelerated rather than initiated the malignant change.

Studies in Humans

Physiologic Effects

Several studies have addressed the short- and long-term effects of marijuana smoking on lung function. While the Δ^9-THC in smoked marijuana initially relaxes airway smooth muscle in both healthy persons[20,21] and stable asthmatic patients,[22] causing bronchodilation, this bronchodilator effect is relatively short-lived and diminishes with the repeated use of marijuana (tachyphylaxis).[23] In contrast to its acute bronchodilator effect, regular marijuana smoking has been shown to cause abnormal decrements in lung function, most likely due to damaging effects on airways having long-term exposure to noxious components within the smoke. After an 11-day period of abstinence, 28 healthy young men who were experienced cannabis users had mild but statistically significant airflow obstruction develop after smoking marijuana ad libitum (mean of 5.2 "joints" per day) for 6 to 8 weeks, and the decrements in lung function were correlated with the average daily amount of marijuana smoked.[23] Cessation of (or reduction in) smoking for a month led to a restoration of the baseline level of lung function, indicating that the mild impairment in airway dynamics caused by several weeks of heavy daily marijuana smoking is reversible.

Recently Tashkin and co-workers compared the lung function of heavy habitual smokers of marijuana alone ($n=144$) or with tobacco ($n=137$), smokers of tobacco alone ($n=70$), and nonsmokers ($n=97$) from the Los Angeles area.[24] The results of this comparison indicated that marijuana smoking was associated with significantly worse values for measures of large airways function, irrespective of concomitant tobacco smoking, whereas tobacco smoking adversely affected the peripheral airways and alveolated portion of the lungs, as reflected by tests of small airways function and the diffusing capacity for carbon monoxide (D_LCO). Repeated tests of lung function in 138 participants in the above study over three to four years continued to show adverse effects of habitual marijuana smoking on large airway function and, in addition, suggested an additive effect of marijuana and tobacco leading to further obstruction in smaller airways.[25]

Similar results were noted in an epidemiologic study of young (15- to 40-year-old) residents of Tucson, Arizona. This study showed functional evidence of airflow obstruction in male smokers of nontobacco cigarettes (mostly marijuana)

which was more prominent than that associated with tobacco smoking.[26] Moreover, the effect of smoking both types of cigarettes concurrently appeared to be additive. These findings suggest that marijuana smoking may be an important factor in young men with functional evidence of obstructive airway disease.

Histopathologic Effects

Fligiel and associates examined bronchial mucosal biopsy specimens obtained by fiber-optic bronchoscopy in 30 young habitual smokers of marijuana only (average of 3 to 4 joints per day), 17 smokers of both marijuana and tobacco, 15 smokers of tobacco only (average of more than 20 cigarettes per day), and 10 nonsmokers.[27] While histopathologic abnormalities in the bronchial mucosa were significantly more common and severe in each group of smokers compared with the nonsmokers, most types of mucosal abnormalities (including basal cell hyperplasia, goblet cell hyperplasia, cellular disorganization, and basement membrane thickening) were more frequent in the marijuana-only than the tobacco-only smokers. Moreover, nearly all the epithelial and basement membrane abnormalities were most commonly observed in habitual smokers of both marijuana and tobacco. These findings suggest that the daily smoking of relatively small amounts of marijuana (3 to 4 joints) has at least a comparable, if not greater, effect on tracheobronchial histopathology than the daily smoking of a much larger quantity of tobacco (more than 20 cigarettes). Further, findings show smoking both marijuana and tobacco produces additive effects on airway injury. The latter observation is consistent with earlier findings by Tennant of histopathologic abnormalities in heavy smokers of hashish or tobacco or both.[28] Whereas all hashish smokers examined by Tennant had respiratory tract symptoms and many had abnormal lung function,[28] most marijuana smokers in whom Fligiel and colleagues observed extensive microscopic changes involving the tracheobronchial epithelium were asymptomatic and had minimal or no lung function abnormality.[27] The latter findings suggest that habitual marijuana smoking causes significant, although clinically silent, airway injury at a relatively early age when symptoms and lung function are absent or relatively uncommon. The potential for the bronchoepithelial histopathology observed in marijuana smokers to progress to clinically symptomatic airways disease and lung dysfunction is as yet unknown, although such progression is certainly possible.[29-31]

Effects on Alveolar Macrophages

Alveolar macrophages are the most populous cells residing in the air spaces and key elements in the lungs' immune defense system. Examination of alveolar macrophages obtained by bronchoalveolar lavage from smokers of marijuana, tobacco, or both and from nonsmokers has revealed significant differences in number,[32] structure,[33] and function (M. Sherman, written communication, January 1990). Barbers and co-workers noted an increase in the number of alveolar macrophages recovered from the lungs of smokers of marijuana, tobacco, or both compared with nonsmokers.[32] Among the marijuana smokers, these increases were independent of concomitant tobacco smoking, although smoking both marijuana and tobacco appeared to have additive effects. Because the increase in the alveolar macrophage population probably represents an inflammatory response to lung injury, these findings imply an adverse effect of marijuana smoking on the lungs that is independent of and additive to that of tobacco.

On ultrastructural examination of the alveolar macrophages recovered from the lungs of the same three groups of smokers and nonsmokers, Beals and associates observed larger and more complex cytoplasmic inclusions in the macrophages of tobacco or marijuana smokers, or both, than in the nonsmokers.[33] They also observed definite ultrastructural differences between the alveolar macrophages of marijuana smokers and tobacco smokers that could indicate differences in the functional activity of these important cells. In this regard, Sherman has recently found notable differences in stimulated superoxide anion release from the alveolar macrophages of tobacco versus marijuana smokers (written communication, January 1990). Sherman has also found an impairment in microbicidal activity of alveolar macrophages from both tobacco and marijuana smokers, presumably due to a smoking-related defect in nonoxidative defense mechanisms. Together with the earlier findings of Huber and colleagues in rat alveolar macrophages,[14] these results imply that marijuana smoking, like tobacco smoking, impairs the lungs' defense against microbial invasion, thereby increasing the tendency to respiratory tract infection.

Effects on Respiratory Tract Symptoms

Few studies have systematically addressed the long-term effects of habitual cannabis smoking on respiratory tract symptoms and disease. The few clinical studies published in the 1970s yielded conflicting results,[34-38] probably because of small sample sizes, nonrandom sampling techniques, and a failure to control adequately for confounding factors, such as concomitant tobacco smoking. More recently, two large-scale studies carried out in Los Angeles[24] and Tucson[26] have shown a significant relationship between habitual marijuana smoking and chronic respiratory tract symptoms. The Los

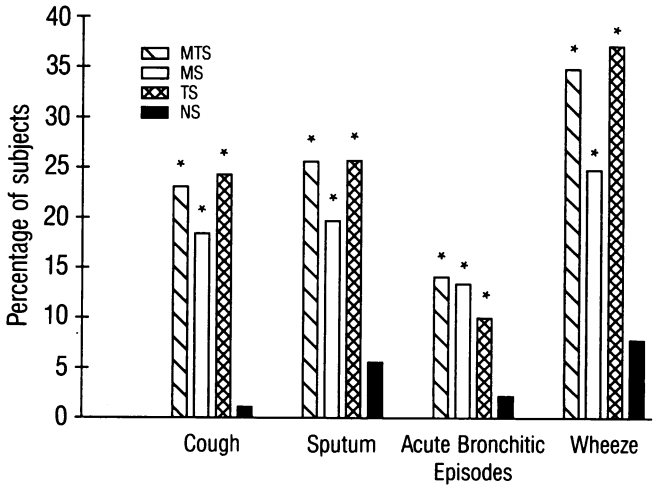

Figure 1.—The graph shows the proportion of smokers of both marijuana and tobacco (MTS), marijuana only (MS), tobacco only (TS), and nonsmokers (NS) with chronic respiratory tract symptoms (chronic cough, chronic sputum production, acute bronchitic episodes, and wheeze). chronic cough = cough on most days for ≥3 months out of the year for ≥2 years, chronic sputum = production of some sputum on most days for ≥3 months out of the year for ≥2 years, acute bronchitic episodes = ≥2 episodes of increased cough and sputum lasting ≥3 weeks within the past 3 years, wheeze = - wheeze on ≥21 days per year, * = significantly different from NS

Angeles group studied a convenience sample of persons who habitually smoked marijuana heavily—more than 10 joints or joint-equivalents per week for more than five years—alone or with tobacco, regular smokers of tobacco only, and nonsmokers.[24] All groups consisted of men and women of roughly equivalent age (25 to 49 years) and socioeconomic status who said they did not have a history of potentially confounding factors, such as chronic respiratory tract disease, hazardous occupational exposures, smoking of cocaine or other illicit substances besides cannabis, or intravenous drug abuse. The results of this study show that those who smoke marijuana regularly have significantly more symptoms of chronic bronchitis (cough, sputum, wheeze) and a significantly greater frequency of episodes of acute bronchitis than do nonsmoking control subjects (Figure 1). No difference in the prevalence of chronic cough, sputum production, or wheeze was found between the marijuana and tobacco smokers despite the markedly different daily quantities of the two substances smoked (3 to 4 joints of marijuana versus 22 tobacco cigarettes). The similar frequency of respiratory symptoms among the two types of smokers despite the notably different numbers of cigarettes smoked per day is surprising. This finding could be due to the greater respiratory delivery of the smoke contents of marijuana compared with the smoke from an equivalent amount of tobacco as a result of differences in filtration and smoking technique, as already noted.[9]

Data from the Tucson epidemiologic study also showed a substantially higher prevalence of phlegm and wheeze in both male and female smokers (n = 100) of nontobacco cigarettes (mostly marijuana), irrespective of concomitant tobacco smoking, compared with never smokers of nontobacco cigarettes.[26] Together the data from these two studies suggest that marijuana smoking may be an important contributing factor to chronic respiratory tract symptoms in young adults.

Other Effects

Barotrauma. Pneumomediastinum has been reported to occur after marijuana smoking.[39,40] These cases of barotrauma were most likely caused by increased intrathoracic pressure due to Valsalva maneuvers during the breath holding after deep inhalation of the smoke, leading to alveolar rupture with dissection of air along the vessels and bronchi to the mediastinum.

Accelerated clearance of plasma theophylline. Hydrocarbon components within the smoke of marijuana, like that of tobacco, can induce hepatic mixed oxidases to accelerate the metabolic clearance of theophylline.[41] As a consequence, the serum theophylline half-life is shortened in habitual marijuana smokers receiving theophylline. In patients treated with theophylline, therefore, it is important to inquire about marijuana- and tobacco-smoking habits because these can influence dosing requirements.

Effects of marijuana contaminants. Contamination of marijuana with *Aspergillus fumigatus* can cause lung disease, as illustrated by case reports of the development of allergic bronchopulmonary aspergillosis in one patient with asthma[42] and invasive *Aspergillus* species pneumonitis in two patients with impaired immunity (one with chronic granulomatous disease and the other after bone marrow transplant for chronic myelogenous leukemia) after smoking marijuana contaminated with the fungus.[43,44]

Cocaine

The use of cocaine in the United States has increased dramatically within the past decade,[4,45] as has the prevalence of the medical complications associated with cocaine intoxication, including central nervous system reactions, catastrophic cardiovascular events, and obstetric complications.[46] According to population estimates based on the most recent national household survey,[4] 2.9% of teenagers (ages 12 through 17 years) and 12.1% of young adults (18 through 25 years) have used cocaine in the past year, whereas 1.4% of teenagers and 4% of young adults use it currently (within the past month). In recent years, smoking of alkaloidal (freebase) cocaine has replaced the nasal insufflation of cocaine hydrochloride as the most common method of use. Freebase cocaine, or crack, obtained by the alkaline extraction of the hydrochloride salt, is more suitable for smoking than cocaine hydrochloride because of its greater volatility and resistance to thermal decomposition. When freebase cocaine is smoked, usually through a water pipe or mixed with tobacco or marijuana in a cigarette, a large amount of the inhaled cocaine is absorbed by the extensive pulmonary circulation. The resultant central nervous system effects are of a similarly rapid onset and equivalent intensity to those following intravenous injection, thus contributing to the growing popularity of this method of use. At the same time, the intoxicating effects of freebase cocaine are of a relatively short duration, leading to more frequent use to maintain the euphoric high. The increasingly widespread use of smoked cocaine raises the possibility of pulmonary complications of inhaling its combustion products. Because the respiratory effects of smoking cocaine have recently been reviewed,[45] I will summarize them only briefly.

Of 19 consecutive habitual smokers of freebase cocaine admitted to a chemical dependence program, most (63%) complained of respiratory tract symptoms, including cough (58%) and shortness of breath at rest or with exercise (58%).[47] Pulmonary function tests in these smokers showed no evidence of airflow obstruction or restriction, but the D_LCO was significantly reduced (less than 70% of predicted in 10 of the 19 subjects), although physiologic responses to steady-state exercise were normal.[48] Although these findings suggest that cocaine inhalation frequently induces respiratory tract symptoms and pulmonary gas exchange abnormalities, most subjects studied also gave a history of smoking tobacco and marijuana, which could have contributed to the observed respiratory abnormalities. Isolated reductions in D_LCO were also reported in two patients admitted to hospital for the treatment of freebase cocaine abuse, but these abnormalities could have been accounted for by concomitant tobacco smoking and previous intravenous drug abuse with pulmonary embolism.[49] In contrast, Tashkin and associates failed to find evidence of diffusion impairment in 16 "moderate" cocaine smokers who also smoked marijuana but did not smoke tobacco or use drugs intravenously.[50] On the other hand, these authors found that the smoking of cocaine appeared to potentiate the adverse effects of tobacco on the airways, leading to substantial airflow obstruction.[47] In the same study, the following acute respiratory tract symptoms were frequently reported in temporal relation to cocaine smoking: black sputum (43%), hemoptysis (14%), and chest pain (79%) that was often pleuritic. Similar acute respiratory tract symptoms have been reported by others.[48,51] The black

sputum has been attributed to the inhalation of a tarry residue from butane torches or matches used to heat the cocaine.

Pneumothorax, pneumomediastinum, or both—the latter previously observed with marijuana smoking[39,40]—have also occurred in several patients after cocaine smoking,[52-55] most likely owing to barotrauma resulting from the extended Valsalva maneuvers associated with cocaine inhalation.

Within the past two years, the following four examples of acute diffuse lung damage have also been reported in temporal proximity to smoking cocaine:

- Noncardiogenic acute pulmonary edema accompanied by dyspnea and hypoxemia that resolved spontaneously within 72 hours[56];
- Bronchiolitis obliterans with organizing pneumonia documented on open-lung biopsy, manifested clinically by fever, nonproductive cough, dyspnea, airflow obstruction, and bilateral nodular opacities on chest x-ray films and responding to corticosteroid therapy[57];
- Recurrent pulmonary infiltrates with eosinophilia over several months, each episode after a bout of cocaine freebasing, manifested by fever, productive cough, wheezing, and dyspnea, and responding to corticosteroid therapy[58]; and
- Biopsy-proven diffuse alveolar hemorrhage (without evidence of vasculitis or the Goodpasture's syndrome) with fever, dyspnea, hemoptysis, and diffuse alveolar infiltrates.[59]

The mechanism whereby cocaine smoking might have caused acute lung injury in these cases is speculative, but suggested mechanisms have included cocaine-induced pulmonary vasoconstriction leading to anoxic cell damage, a direct toxic effect of the cocaine alkaloid on alveolar capillary endothelium, and a hypersensitivity reaction to components in the freebase smoke.

Another possible pulmonary complication of freebase cocaine is severe thermal injury to the conducting airways due to intratracheal ignition of the ether used in the freebasing process. In the one published case report, the thermal injury to the lower airways led to severe reactive airways disease and tracheal stenosis requiring surgical reconstruction.[60] Finally, cocaine smoking has been reported to cause or contribute to asthma, most likely as a result of nonspecific irritation of the airways.[61]

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